REMARKS

Claims 2-9 are pending in this application. Claim 1 has been cancelled, claims 2-6 have been amended, and claims 7-9 have been added. Support for this amendment and for the new claims is found on page 12 of the specification and in figure 1. The specification has been amended to correct grammatical errors. No new matter has been added.

Rejection under 35 U.S.C., § 112, first paragraph

Written Description

The Office rejected claims 1-6 as failing to comply with the written description requirement of 35 U.S.C. §112. Applicant respectfully traverses.

The Office argues that the written description provided in the specification is insufficient to demonstrate possession of the claimed invention because no representative species of the genus is disclosed by presenting its amino acid sequence and sequence identification number. *Office Action,* page 3. The Office concludes that without a sequence listing of the sequence to be mutated, Applicant had no possession of the claimed invention. *Office Action,* page 4.

In the present application, Applicant claims human antithrombin variants. The specification identifies natural antithrombin III as the protein to be modified. *Specification,* page 1. Information which is well known in the art need not be described in the detail in the specification, MPEP § 2165(II)A(2), and here, the protein sequence of natural human antithrombin III is well known in the prior art. *See, e.g.,* F. Tokunaga *et. al., J Biochem*, 116,1164-70 (1994); Chandra et al., *Proc Natl Acad Sci*, USA 80, 1845-1848 (1983); Koide, T., *J. Biochem* 86, 1841-1850

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

(1979). Because a person skilled in the art would recognize that Applicant had possession of the claimed antithrombin III variants by reading the specification in light of the fact that the amino acid sequence of natural antithrombin III was known in the art, Applicant meets the written description requirement without specifically reciting the amino acid sequence of natural antithrombin III. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Enablement

The Office rejected claims 1-6 for lack of enablement under 35 U.S.C. §112, first paragraph, arguing that without further guidance on the part of Applicant as to the sequence of the human antithrombin to be modified, undue experimentation is needed to practice the invention. *Office Action,* page 5. Applicant respectfully traverses.

Throughout the specification, Applicant uses the term "natural human antithrombin" to describe the protein to be modified. *See, e.g., Specification,* page 1, line 26; page 2, lines 1, 10, 19, and 25; page 3, lines 3, and 18. As discussed above, the amino acid sequence of natural human antithrombin III is well known in the art. The specification also identifies both the amino acid positions and the amino acid substitutes required to create the claimed antithrombin variants. Applicant, therefore, has provided an enabling disclosure by identifying (1) the protein to be modified; (2) the specific amino acid positions to be modified; and (3) the specific amino acids one of skill in the art should use to modify the disclosed protein at the disclosed positions. As a result, no undue experimentation would be necessary to practice the invention. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Rejection under 35 U.S.C. §102

The Office rejected claims 1 and 6 as anticipated by J.A. Huntington *et.al.*, *Biochemistry*, 1998, 37, 3272-3277 under 35 U.S.C. §102. Applicant has cancelled claim 1, and has amended claim 6 and added new claims 7-9 depending from claims 2-5, respectively. Huntington teaches only the replacement of one amino acid with cysteine. Cysteine is not one of the amino acids identified in amended claims 2-5. Therefore, neither claim 6 nor new claims 7, 8 and 9 are anticipated by Huntington. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Rejection under 35 U.S.C. §103

The Office rejected claim 5 under 35 U.S.C. §103 as obvious in light of J.A. Huntington *et.al.*, *Biochemistry*, 1998, 37, 3272-3277, J.A. Huntington *et.al.*, *Biochemistry*, 1996, 35, 8495-8503, and common knowledge in molecular biology. Applicant respectfully traverses.

To establish a case of obviousness, the Office must show that there is a motivation to combine the references cited against the application, that there is a reasonable expectation of success, and that the prior art teaches all of the claimed limitations. MPEP, § 2143. The Office argues that motivation to combine the teachings of Huntington with alternate amino acid substitutions to create the claimed heparin-independent antithrombin variants is found in Huntington. *Office Action,* page 8. According to the Office, Huntington states that the regulation of the inhibitory action of antithrombin III by heparin binding "accounts both for the occurrence of thrombosis in patients whose antithrombin has a defect in heparin binding or activation and for the widespread clinical use of exogenous heparin as an

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

anticoagulant." *Huntington,* 1998, page 3272. Based on this language, the Office states that "one skilled in the art would be motivated to obtain antithrombin that is more clinically useful by making it independent on its activator, heparin." *Office Action,* page 8.

This language provides no motivation to substitute amino acids, other than cysteine at position 380 of antithrombin III. Huntington teaches that cysteine is sufficient to create a heparin-independent variant. Thus, while Huntington may provide motivation to create a clinically-useful variant by substituting cysteine at amino acid position 380, a person skilled in the art would not find motivation in Huntington's success to try other amino acids. Huntington provides insufficient motivation to combine elements of the prior art to produce the claimed invention.

The Office also states that "the expectation of success was very high, because Huntington et al teach that position 380, having functional symbol P14, needs to be displaced from beta-sheet A of the protein to render it heparin independent." *Office Action*, page 8. This argument is undercut by Huntington's 1996 paper. In his 1996 paper, Huntington states that the inhibitory action of antithrombin III is "very sensitive to the correct folding of antithrombin." J. A. Huntington *et.al.*, "Mechanism of heparin activation of antithrombin. Evidence for reactive center loop preinsertion with expulsion upon heparin binding," *Biochemistry* 1996, 35, 8495-8503 at page 8498. Any mechanism that exhibits a high level of structural sensitivity is likely going to be similarly sensitive to changes to its structure. Accordingly, a person skilled in the art would know that substituting alternate amino acids into known functional sites of antithrombin III would not necessarily be successful.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Finally, the cited references disclose antithrombin variants substituted with cysteine and tryptophan. Claim 5 recites substitution with alanine, aspartic acid, glycine, histidine, isoleucine, leucine, asparagnine, proline, arginine, threonine, tyrosine, and valine. The Office has not cited any reference that uses any of the claimed amino acids in an antithrombin variant. As a result, not all of the claimed limitations are taught by the prior art cited by the Office.

Because the cited references contain no suggestion to combine their teachings, they provide a person skilled in the art with no expectation that substituting amino acids into antithrombin III will be successful, and they contain no teaching of all claim limitations, Applicant respectfully requests that the rejection be withdrawn.

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 28, 2003

By: _____
Carol P. Einaudi
Reg. No. 32,220

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com